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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/627,775	07/28/00	GREENE M	UPN-3832

EXAMINER	
GHASHGHAEE,F	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/627,775	GREENE ET AL.	
	Examiner	Art Unit	
	Fariba Ghashghaee	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-48 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-48 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6&7 .

18)☐ Interview Summary (PTO-413) Paper No(s). _____ .

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment in vitro using the WP9QY peptide, does not reasonably provide enablements for treatments using other peptides or for in vivo treatments in patients. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broadly drawn to methods of inhibiting steoclastogenesis,treating patients who have bone loss by inhibiting bone loss, and treating patients to inhibit bone resorption using inhibitors. The specification provides some guidance on making a variety of different inhibitors as shown on pages 27-30. The specification provides absolutely no specific guidance on methods of selection, identification or use of any inhibitor from the literally billions of possible inhibitors suggested by dependent claim 2 which would function to achieve inhibition of osteoclastogenesis, treatment of bone loss or treatment to inhibit bone resorption. Further, the specification, while giving generic advice on patient treatment, fails to give any specific information on how to treat patients with particular inhibitors to achieve the goal of reducing bone loss or inhibiting bone resorption. In particular, the examiner notes that the narrowest dependent claims

ultimately require SEQ ID NOs: 12-15 to function as the inhibitors. There is, however, only a single working example showing the effect of an inhibitor to achieve the goal of inhibition of osteoclastogenesis, which is SEQ ID NO: 13, WP9QY. There are no working examples of the use of any inhibitor in patients, or indeed, in multicellular organisms. There is prior art which teaches that certain specific sequences in the TNF superfamily function to inhibit osteoclastogenesis such as Yamaguchi et al (J. Biol. Chem. (1998) 273(9):5117-5123) who teaches that the first four domains of OCIF function to inhibit osteoclastogenesis. While the level of skill in the art is high, it is extremely unpredictable which alterations in the peptide sequence of WP9QY or what other sequences would function to inhibit osteoclastogenesis and would function to treat, in patients, bone loss or inhibit bone resorption. As Yamaguchi further states "However, the biological activity of the mutants was not accuractely determined in their study (page 5122, column 2)". Yamaguchi here shows the level of unpredictability in identifying alterations which function to inhibit osteoclastogenesis since a previous study found a loss of activity by mutants of OCIF. Yamaguchi shows that these mutants have activity at a reduced level of OCIF. This demonstrates that even among those skilled in the art, it is unpredictable whether specific alterations will have specific inhibitory effects on osteoclastogenesis. Further evidence of the unpredictability of protein inhibitors in bone marrow cells is provided by Kitazawa et al, (J. Clin. Invest. (1994) 2397-2406) who argues that IL-1 and TNFbp affect bone resorption. Kitazawa states "Assays of cytokines in the culture media of bone marrow cells revealed that ovx is associated with an increased production of IL-1 and TNF, a finding in keeping with previous rat and

human studies of ours and others, bun in contrast with those of Hustmyer et al and Zarrabeitia et al who failed to detect a higher production of IL-1 and TNF in osteoporotic women. We also found that ovx was not associated with an increased bone marrow cell production of IL-6. This is agreement with the studies of Chaudhary et al, Rifas et al and Rickard et al, but in contrast with that of Jilka et al who documented an increased production of IL-6 (page 2402, columns 1 and 2)". This statement clearly shows that different systems yield different results which are unpredictable. In particular, it shows tha the ligands involved in causing bone resorption and bone loss are unpredictable. Separately, the differential results between rat and human studies and studies of osteoporotic women show that the unpredictability in applying results from one system to another. Here, without any evidence of efficacy, applicant would purport to apply the results of an in vitro system which has only one functional inhibitor to human therapeutics. Lastly, Takasaki et al (Nature Biotech. (1997) 15:1266-1270) teaches a variety of difficulties in applying the compounds at issue for human therapy. Takasaki notes clear disadvantages regarding large macromolecules such as "poor bioavailability and stability, expense, and risk of severe and occasionally life-comprimising side effects (page 1266, column 1). Takasaki further notes regarding small peptides that "most TNFalpha antagonistic peptides obtained to date have been large and relatively insoluble (page 1266, columns 1 and 2)". Lastly, with regard to the unpredictability relative to the sequence, Takasaki creates approximately 18 different peptides, but finds that only one gives near wild type levels, and only three more give substantial inhibition. This further demonstrates the unpredictability of alterations within the peptide sequence

regarding the retention of activity for inhibition or other functional effects. For the reasons and evidence given, such a change would be extremely unpredictable. The quantity of experimentation to test the billions of different possible inhibitors in both the in vitro and in vivo system would be unmanageably high. It would require inventive experimentation with each positive result functioning as an unexpected result and would require many thousands of man hours to analyze even a fraction of the inhibitors which fall within the scope of the claims.

Therefore, given the broad claim, the minimal teaching in the specification, the presence of only a single working example, the lack of teaching of the broad inhibitor class in the prior art, the unpredictability of the art and the large amount of experimentation necessary to reduce the unpredictability, balanced only be the high skill level in the art, it is concluded that undue experimentation is required to make and use the invention as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16, 17-32, and 33-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

claim 1 and its dependent claims 2-16 are rejected because in claim 1, the

terms " inhibiting osteoclastogenesis" and "an amount of an inhibitor effective to inhibit osteoclastogenesis" and in claim 17 and its dependents claims 18-32, the terms "diseases characterized by bone loss" and again "an amount of an inhibitor effective to inhibit such bone loss" and in claim 33 and its dependents claims 34-48, the terms "inhibiting bone resorption" and again "an amount of an inhibitor effective to inhibit bone resorption", do not clearly recite the exact level of inhibition, for example inhibits all the symptoms or some of the symptoms, or inhibits for a short period of time or increase the survival of the patient for a long period of time or cures the diseases, and therefore, it does not specifically and distinctly define the claims.

In claims 2, 5-7, 9-11, 13-15, 18-21, 23-25, 27-29, 34, 37-39, 41-43, and 45-47, two different symbols, " ≡ " and " =" are used to define the same concept of covalent linkage, which makes the claims unclear.

The appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 17, and 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Stahl et al.(US Pat. No. 5,470,952).

Stahl et al. discloses a method for inhibiting osteclastogenesis, bone loss, osteoprosis and also for inhibiting bone resorption (See column 3, lines10-14, column 9, lines 28-44, Abstract and claims 1-2).

Claims 1, 17, and 31-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamaguchi et al. (" Characterization of Structural Domains of Human Osteoclastogenesis Inhibitory Factors", J. Biological Chemistry, 1998, 273(9), 5117-23).

Yamaguchi teaches a method for inhibiting osteoclastogenesis, and bone loss by reciting that osteoclastogenesis inhibitory factor (OCIF) is a heparin-binding secretory glycoprotein that belongs to the tumor necrosis factor (TNF) family. OCIF is present both as a ~60 kDa monomer and a disulfide-linked homodimer. Their results show that: The N-terminal portion of OCIF containing domains 1-4, which have structural similarity to the extracellular domains of the TNFR family proteins, is sufficient to inhibit osteoclastogenesis. (See Abstract, Figures 1 and 2 on page 5119).

Claims 8, 22, and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Takasaki et al.(" Structure-based design and characterization of exocyclic peptidominetics that inhibit TNFα binding to its receptor, " Nature Biotechnology, 1997, 15, 1266-1270).

Takasaki teaches 18 different peptides with different sequences including SEQ.ID. NO.13, WP9QY, and also teaches the inhibitory activities of these peptides (See Page 1267, table 1, and figure 1).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4, 9, 17-19, 23, 31-36, and 41 are rejected under 35 U.S.C. 102(a) as being anticipated by Cheng et al.(US Pat. No. 5,849,865).

Cheng et al. discloses a method for inhibiting osteoclastogenesis, bone loss, osteoprosis, wherein the inhibitor comprising a peptide of variety number of amino acid residues which is bonded to different sequences and includes moieties with hydrophobic and hydrophilic characteristics. Cheng has included peptides with 3-18 and 1-6 amino acids that at least one of which is a hydrophobic amino acid. Cheng also disclosed sequences similar to the sequences of the claimed invention (See column1, lines 29-47, and also in claim 6, SEQ. ID. NOS: 26-27).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al. (" Characterization of Structural Domains of Human steoclastogenesis Inhibitory Factors", J. Biological Chemistry, 1998, 273(9), 5117-23) and further in view of Green et al.(WO 98/53842).

Yamaguchi teaches a method for inhibiting osteoclastogenesis, and bone loss by reciting that osteoclastogenesis inhibitory factor (OCIF) is a heparin-binding secretory glycoprotein that belongs to the tumor necrosis factor (TNF) family. OCIF is present both as a ~60 kDa monomer and a disulfide-linked homodimer. Their results show that: The N-terminal portion of OCIF containing domains 1-4, which have structural similarity to the extracellular domains of the TNFR family proteins, is sufficient to inhibit osteoclastogenesis. (See Abstract, Figures 1 and 2 on page 5119).
Claims are different from Yamaguchi in the citation of the peptide inhibitors with 3-18, 1-6, 1-3, and 1-2 amino acids.

Green et al. teaches peptide and peptide analogues designed from a binding loop of a member of the tumor necrosis factor receptor (TNF-R) superfamily. In particular their invention relates to cyclic peptides and peptide analogues designed from

a binding loop of TNF-R which inhibit TNF binding to its cellular receptors, and methods of making and using such compounds to inhibit the biological activities of TNF.(See Abstract). Green teaches the composition of an inhibitor which has a peptide of 3-18 amino acid residues corresponds in primary sequence to a binding loop of a TNF-R superfamily member with all the limitations of the claimed invention.(See Page 4, lines 21-36 and Page 5 lines 1-19). Green also teaches an inhibitor which has the same skeletal structure with a peptide of 1-6 amino acids that at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety which has all the limitations of the claimed inventions(See Page 23, lines 25-36and page 24, page 25, lines 1-14 and Page 27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the TNF-R superfamily osteoclastogenesis inhibitors taught by Yamaguchi with TNF receptor-derived peptides and peptide analogues of Green to make the claimed inhibitory peptides and use it to treat osteoclastogenesis.

The person of ordinary skill in the art would have been motivated to make these inhibitory peptides to treat osteoclastogenesis, and would have been expected reasonable level of success because Yamaguchi teaches that by analyzing the osteoclastogenesis inhibitory activity of deletion and C-terminal truncation mutants, he found that the N-terminal portion containing domains 1-4 is sufficient to inhibit osteoclastogenesis. Domains 1-4 correspond to the extracellular cysteine-rich regions of the TNFR family proteins (See page 5122, column 1, last paragraph).

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fariba Ghashghaee whose telephone number is (703)305-3586. The examiner can normally be reached on 8:30-4:30 Mon.-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703)308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703)305-3014 for regular communications and (703)305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

Fariba Ghashghaee
Examiner
Art Unit 1656

Fariba Ghashghaee

May 5, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

5/7/01